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NEW TRENDS FOR VACCINE PRODUCTION AND UNIDO PROGRAMME ON INDUSTRIAL PRODUCTION OF BIOLOGICALS

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The needs of developing countries for the production of biologicals are recently acquiring great urgency. At present there are worldwide some twenty producers of polio and measles vaccines, thirty manufacturers of BCG, forty laboratories that prepare DPT and close to seventy that produce tetanus toxoid, however only a few companies take part regularly in competitive biddings of UNICEF and PAHO providing vaccines for the Expanded Programme on Immunization (EPI) of WHO. In other words, through the above UN agencies, more than 275 million doses of EPI vaccines produced by a few large manufacturers were supplied in 1984 to approximately one third of 90 million children born in more than 130 developing countries in the world (1,2). In order to achieve the goal of EPI, that is providing immunization services against diphtheria, whooping cough, tetanus, measles, tuberculosis and poliomyelitis for every child by 1990, 5-7 times more vaccines would be required. To meet the above increased demand, the existing capacities of the main suppliers of the EPI would have to be enlarged. However, it must be noted that the biological industry, this small but important part of the pharmaceutical industry has some special characteristics such as that, apart from the uncertaintities of the international competitive bidding, it is a high-risk, low-return venture (3). If creation of new capacities for vaccine production would be required in the biological industry, UNICEF most probably will not be able to keep the present low prices (4).

An obvious alternative solution to assure the continuous supply of EPI vaccines is to undertake production in the developing countries at national, subregional and regional level. Several developing countries like Brazil, Colombia, Cuba and Mexico in Latin-America, India, Indonesia and Pakistan in Asia, Algeria and Egypt in Africa have already started an extensive programme on domestic production of vaccines. This is also reflected by the increased number of requests from developing countries for UNIDO's Technical Assistance in this particular subsector of the pharmaceutical industry. Towards this end UNIDO has decided to launch a programme on industrial production of biologicals (IPB). An Advisory Panel on Preventive Medicine has been established and it is considered essential to provide advice and guidance in this field to UNIDO (5).

The strategy of the IPB programme is based on an industrial approach characterized by the concept of unit process and homogenous culture system. This approach also secures the consistency in the

consecutive production lots by means of a built-in quality assurance. It advocates the required transfer of technology through a long-term support programme to make the recipient enable to adopt and assimilate the technology but also to assist in the promotion of new products.

In line with the conclusions and recommendations given by the Second Consultation on the Pharmaceutical Industry in Issue 4: Biologicals, the UNIDO Advisory Panel on Preventive Medicine, in its first meeting, in 1984 recommended that a study should be prepared on the impact of modern technologies on production during the forthcoming decade of priority vaccines (6,7). This study, the "Model Programme for the Production of Vaccines in Developing Countries" is intended primarily for use by Government officials and directors of institutes, responsible for framing and implementing national vaccination programmes. In addition it can be used as guidance by professional staff members responsible for implementing the programmes. It can also serve as a base for comparison of different technologies applied in other laboratories for production and control of conventional vaccines.

The Model Programme summarizes the experience of a single manufacturer, namely the Rijksinstituut voor Volksgezondheid en Milieuhygiene (National Institute of Public Health and Environmental Hygiene, abbreviated as RIVM), Bilthoven, the Netherlands, in the production and quality control of conventional vaccines. It thus offers only one choice of a number of existing technologies. It is nonetheless a well proven technology considered to be in the forefront in some areas of vaccine production.

Since the era of Pasteur and Koch, the technologies of vaccine production have been developed more in an empiric way than by systematic R&D, thus making even industrial scale production more akin to cookery (8). In many countries it has been consigned to governmental institutes. In fact, with some notable exceptions, pharmaceutical industries have become less interested in making the large investments in improving the production and quality control techniques of vaccines and other biologicals. As a result, insufficient use is often made of scientific developments in the fields of biochemistry and biochemical engineering, immunology, microbiology, virology and animal husbandry. In particular, the manufacturing process is often ill defined and even

obsolete. In some instances this will yield relatively crude products (an example is pertussis vaccine), and in addition there is poor consistency between consecutive production lots. In many cases the production process is still largely manual. This leads to a vicious downward spiral where low technology leads to a lack of intellectual stimulation and research. It should be emphasized that, in spite of the rather limited investments made in the development of conventional vaccines, the Expert Committee on Biological Standardization of WHO has established a number of excellent standards and reference materials, as well as international requirements for vaccines which are widely used. These have certainly guided many countries in the production of vaccines of acceptable quality. In the case of smallpox vaccine, the quality control programmes of WHO have contributed to the world wide eradication of this disease.

In recent years a number of developed countries have introduced a new form of quality control. In addition to using as reference the standards established by WHO for laboratory facilities for the control of vaccines and sera, they have instituted methods in compliance with rules for Good Manufacturing Practice (GMP) that have been formally drawn up in recent years (9,10). These rules include procedures for the qualification of personnel and their on-the-job training, the establishment and maintenance of building facilities and equipment for production, control and formulation, and the necessary control of raw materials.

GMP procedures established for the production of conventional vaccines will be generally applied to the growing field of biotechnology, regardless of whether the end product will be used in human or veterinary medicine, agriculture or in industrial processes.

One of the basic concepts of the Model Programme, the unit process was originally proposed by van Hemert (11). The main vaccines considered in the Model Programme are all made using the same basic system employing a stainless steel bioreactor unit (the Bilthoven Unit) which can be sterilized in situ and controlled for parameters concerned with microbial cell growth (12). These include pH, pO_2, pCO_2; also sampling to determine growth, opacity and titre of the required biological products. The use of the Bilthoven Unit allows the same conditions to be maintained during scale-up and greatly improves the consistency of the process. In the beginning it

could not be used for virus cultivation, which requires as substrate mammalian cells obtained from animal organs (e.g kidneys) or consisting of so-called cell strains or cell lines. The microcarrier system developed subsequently by van Wezel at the RIVM made it possible to grow large quantities of mammalian cells on the surface of plastic-like particles, which could be held in suspension in the Bilthoven Unit (13). Large amounts of virus materials can thus be obtained, while modern purification procedures ensure the effective removal of contaminating substances yielding an end product with acceptable levels of impurities including RNA or DNA.

The use of (semi-)industrial techniques, such as the unit processing for production of conventional vaccines, will no doubt be stimulated by the simultaneous introduction of GMP. In the Model Programme it is shown how relatively small amounts (in term of human doses) of different vaccines can be prepared in consecutive production rounds with the same facilities and personnel, provided the GMP-rules are strictly observed. There appears to be no principal objection, for instance, to using in the more distant future the same building facilities and equipment for the production of tetanus toxin and BCG vaccine.

While originally cell lines were not permitted for the cultivation of virus materials for human use (even if inactivated), there is at present a tendency favouring their acceptance for human vaccine production.

It could be argued that the existence of facilities for the production and quality control of conventional vaccines will contribute to a number of inter-related, social and economic objectives: reduction of dependance on supplies; increase of domestic stocks of technical know-how and human capital in many disciplines used in development of biologicals and creation of employment.

The advantage of the Model Programme is that the industrial approach taken allows its application for the production of vaccines and other biologicals developed by new biotechnological methods (e.g. recombinant deoxyribonucleic acid (rDNA) and cell fusion). The pharmaceutical, chemical and food processing industries, in that order, are most likely to take advantage of advances of the new biotechnology. Other industrial sectors that will also be affected, although not as immediately, are the mining, crude oil recovery and pollution control industries. Since fermentation is an indispensable element of biotechnology's support system, the experience

gained through the eventual implementation of the UNIDO Model Programme could be utilized in nearly all the products of biotechnology.

In past decades some developing countries have on the basis of the existing scientific organization established regular educational programmes at university level, to create a nucleus of scientists. This has enabled them to make further considerable progress in absorbing scientific knowledge. Among those countries there are now several where capable and intelligent young investigators can follow, or themselves take part in the generation of new knowledge. The major scientific research of these centres is at present still concentrated in the developed world and knowledge is acquired there at an increasing rate. On the other hand, in only a few developing countries are the "knowledge community" structured in such a way that new knowledge is not only absorbed in the academic centres, but also that it can be put to practical use for the benefit of the community. UNIDO's IPB programme provides transfer of technology through a long-term technical assistance programme, which intends to motivate the staff of the centres for academic research to turn towards application, and such a way widens the scope of activity of the conventional production units of biologicals.

Although the pharmaceutical industry was the last to adopt traditional fermentation technologicals, it has been the first industrial sector to make widespread use of the genetic engineering technologies such as the rDNA and cell fusion.

The genetic engineering of biological systems for the production of pharmaceuticals and biologicals has two general goals:

1. To increase the yield of a pharmaceuticals produced, such as the genetic improvement of the strain of Penicillium chrysogenum for penicillin production; and,

2. To produce entirely new pharmaceutical or biologicals such as polypeptides and proteins that are otherwise scarce (peptide hormones, enzymes, vaccines, antibodies, plasma proteins, interferons,etc.)

Some of the important biologicals already produced or to be produced in the near future are as follows:

1. Vaccines: Hepatitis B vaccine
   Herpes simplex vaccine
   Foot and mouth disease vaccine (FMDV)
   Cholera vaccine

2. Hormones: Insulin
   Growth hormone
   Atriopeptin
   Growth hormone releasing factor
   Beta-endorphin

3. Lymphokines: Interferon, alpha
   beta
   gamma
   Interleukin - 2 (IL-2)
   Tumor necrosis factor (TNF)

4. Enzymes: Tissue Plasminogen activator (TPA)
   Urokinase

5. Coagulation proteins : Factor VIII

6. Human plasma proteins: Albumin

7. Other proteins: Protein A

8. Monoclonal antibodies: For cancer treatment
   For cancer diagnosis
   Antitoxin

If application of rDNA technology becomes a real alternative for large-scale production of plasma proteins, the costs are likely to come from purifying the proteins rather than from producing them. For plasma products such as albumin, approximately 300 tons will have to be manufactured and purified. For products such as Factor VIII, such large amounts will not be required, but purification techniques that will not inactivate this highly unstable enzyme will have to be developed. The world market for both proteins prepared by rDNA technology has been estimated to be as high as US$ 2 billion (14).

Recently rapid and significant progress has been made in the development of vaccines against leprosy and malaria. Hence, there are over 10 million leprosy patients in the world, while more than 350 million people are living in areas, mostly in Africa, where malaria is still highly endemic and where no specific antimalaria measures are being applied, the R&D of vaccines and immunotherapy has great importance (15).

The exciting area of new biotechnology offers almost countless possibilities for R&D of future vaccines. Most probably the vaccines used in the year 2000 will be entirely different from the conventional vaccines administered today. Some of the presently used vaccines are deficient in one or more properties. Specific R&D approaches for new biotechnology vaccines include:

1. New and improved methods for polypeptide synthesis : Synthetic vaccines.

2. Antigens expressed by rDNA in prokaryotic (E. coli) or eukaryotic cells (yeast or mammalian cells) : Purified antigens and subunit vaccines.

3. Modification of microbial genomes for the production of stable, safe, attenuated mutants : Live vaccines.

4. Controlled antigen expression in suitable vector organisms : Recombinant vaccinia viruses for vaccine antigens.

5. New ways of antigen presentation : Antiidiotype vaccines.

6. Carrier proteins for peptide antigens : Antifertility vaccine.

7. Augmentation of protective immune responses : Immunological adjuvants and immunomodulators.

It was almost 200 years from Jenner's discovery of smallpox vaccine to the eradication of this disease in 1977. It is a considerable period of time, which might hopefully be significantly reduced in the case of other

vaccines such as polio or measles. Based on the experiences gained in WHO'global eradication programme of smallpox, a combined approach of improving quality of vaccines, transfer of technology and improving the delivery system might bring the earliest success. Through its IPB programme, UNIDO wish to play the role of catalyst for the transfer of technology between holders and recipients, and with all its competence is ready to assist developing countries in assimilating new technologies and achieving a viable production of standard quality products.

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